UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,640	04/08/2004	Wayne M. Coco	3530.1000 US1	8470

38473 7590 01/10/2006

ELMORE PATENT LAW GROUP, PC
209 MAIN STREET
N. CHELMSFORD, MA 01863

EXAMINER	
WOODWARD, CHERIE MICHELLE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,640	COCO ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' Amendment of 31 October 2005, is acknowledged. The Declaration filed on 31 October 2005 under 37 CFR 1.312 has not been entered. See MPEP 715.01(c) for a discussion of the requirements for a 37 CFR 1.312 declaration. Where the applicant is one of the co-authors of a publication cited against his or her application, he or she may overcome the rejection by filing an affidavit or declaration under 37 CFR 1.131. Alternatively, the applicant may overcome the rejection by filing a specific affidavit or declaration under 37 CFR 1.132 establishing that the article is describing applicant's own work. An affidavit or declaration by applicant alone indicating that applicant is the sole inventor and that the others were merely working under his or her direction is sufficient to remove the publication as a reference under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). See MPEP 715.01(c). The Declaration filed under 37 CFR 1.132 on 31 October 2005, has been fully considered, but is not persuasive to overcome the rejection of claims 1-7 based upon anticipation by Coco *et al.*, because the Declaration is merely a sworn statement of derivation of work and lacks any statement to disavow the work of others (*i.e.* the co-authors who are not inventors) identified as co-authors in the paper by Coco *et al.*

The Amendments to claims 1, 3, 4, 5, 6, and 7 have been entered. Claims 1-7 are pending and under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

2. Information Disclosure StatementThe information disclosure statement (IDS) submitted on 21 September 2005 has been considered by the Examiner. A signed copy is attached hereto.

Response to Arguments

Claim Objections/Rejections Withdrawn

3. Applicants' Arguments and Amendments, see Remarks, filed 31 October 2005, with respect to the lack of description of the title of the invention have been fully considered and are persuasive. The objection to the title has been withdrawn in light of Applicants' amendment to the title.

4. Applicants' Arguments and Amendments, see Remarks, filed 31 October 2005, with respect to the rejection of claim 2 under 35 U.S.C. 112, first paragraph, for scope of enablement and written description, have been considered and are persuasive. The rejection of claim 2 under 35 U.S.C. 112, first paragraph, scope of enablement has been withdrawn.

New Claim Objections – Necessitated by Amendment

5. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Objections/Rejections Maintained

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. The rejection of claims 1 and 3-7 under 35 U.S.C. 112, first paragraph, scope of enablement, a being enabling for the protein of SEQ ID NO: 2, does not reasonably provide enablement for all variants of SEQ ID NO:1 with 90% or greater homology, is maintained for the reasons of record in the Office Action of 5 August 2005 and as stated herein.

The claims recite an epidermal growth factor polypeptide having at least 90% amino acid identity to SEQ ID NO: 1 and having epidermal growth factor biological activity in cell proliferation or receptor binding that is greater than the biological activity of SEQ ID NO:1, the EGF polypeptide of claim 1 that has a biological activity in cell proliferation or receptor binding that is at least two, five, ten, fifty, and 100 times greater than the biological activity of the polypeptide of SEQ ID NO: 1.

Applicants argue that the embodiment of SEQ ID NO: 2 provides sufficient guidance to those skilled in the art to develop other variants of SEQ ID NO: 1 without undue experimentation. Applicant argues that SEQ ID NO: 1 is sufficiently small to permit mutation and synthesis with presently available mutation technology and peptide synthesizers to provide a library of variants of SEQ ID NO: 1. Applicant also argues that the EC50 for SEQ ID NO: 2 shows that SEQ ID NO: 2 is more active than SEQ ID NO:1. Additionally, Applicant states that the Examiner's concern is not understood as the activity of SEQ ID NO:2 is not predicated on its ability to displace EGF from its receptor. Applicants' arguments, filed 31 October 2005, have been fully considered but they are not persuasive.

Applicants' argument that SEQ ID NO: 1 is sufficiently small to permit mutation and synthesis to test for EGF variants with either EGF cell proliferation activity or EGF receptor binding activity is merely an invitation for further experimentation. There is no guidance in the specification to teach one of ordinary skill in the at which amino acids can be substituted in the EGF homolog variants so that the variants will retain either of the stated alternative biological activities.

The assertion that unspecified amino acid variants of SEQ ID NO: 1 have cell proliferation or receptor binding biological activities similar to known wild-type EGF cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (see, for example, Benjamin et al., 1998, Development 125:1591-1598; Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic *et al.* (1996, PNAS USA 93:9021-9026), disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also, for example, Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (see, for example, Pilbeam *et al.*, 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick *et al.* (U.S. Patent 5,350,836), for example, disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct

function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks *et al.* (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi-functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith *et al.* (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork *et al.* (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polypeptide variants with 90% amino acid identity to SEQ ID NO: 1 with either cell proliferation or receptor binding activity without resorting to undue experimentation.

Due to the large quantity of experimentation necessary to determine all of the different species of the disclosed polypeptide variants with 90% amino acid identity to SEQ ID NO: 1 such that it can be determined how to use the claimed polypeptide variants, the lack of direction/guidance presented in the specification regarding same, the absence of more than one working example directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The rejection of claims 1 and 3-7 under 35 U.S.C. 112, first paragraph, scope of enablement, a being enabling for the protein of SEQ ID NO: 2, does not reasonably provide enablement for all variants of SEQ ID NO:1 with 90% or greater homology, is maintained for the reasons of record in the Office Action of 5 August 2005 and as stated herein.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

7. The rejection of claims 1 and 3-7 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, is maintained for the reasons of record in the Office Action of 5 August 2005 and as stated herein. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite an epidermal growth factor polypeptide having at least 90% amino acid identity to SEQ ID NO: 1 and having epidermal growth factor biological activity in cell proliferation or receptor binding that is greater than the biological activity of SEQ ID NO:1, the EGF polypeptide of claim 1 that has a biological activity in cell proliferation or receptor binding that is at least two, five, ten, fifty, and 100 times greater than the biological activity of the polypeptide of SEQ ID NO: 1.

Applicants argue that the possession of SEQ ID NO: 2 exemplifies possession of the broader genus. Additionally, Applicants argue that the presently claimed invention is distinguishable from case law such as *Vas Cath, Fiers*, and *Fiddes*. Applicants assert that their description of a variant of SEQ ID NO: 2 meets the written description requirement for the full breadth of the present claims and that no more is required. Applicants' arguments filed 31 October 2005 have been fully considered but they are not persuasive.

Applicants mistakenly confuse the enablement requirements under *In re Wands* with the written description guidelines as stated in *Vas-Cath Inc. Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., an epidermal growth factor polypeptide having at least 90% amino acid identity to SEQ ID NO: 1 and having epidermal growth factor biological activity in either cell proliferation or receptor binding.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties,

functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* SEQ ID NO: 2 (EGF21). The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. Applicants' argument that SEQ ID NO: 1 is sufficiently small to permit mutation and synthesis to test for EGF variants with either EGF cell proliferation activity or EGF receptor binding activity fails to provide an adequate description of all of the potential variants with the requisite alternative activity. Applicant has not adequately described all possible variants with either specified biological activity in any species.

There is substantial variability among the species. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is an EGF polypeptide with 90% amino acid identity to SEQ ID NO: 1. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The rejection of claims 1 and 3-7 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, is maintained for the reasons of record in the Office Action of 5 August 2005 and as stated herein.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The rejection of claims 1-7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the reasons of record in the Office Action of 5 August 2005 and as stated herein. The claims have been amended in part to recite two specific biological activities. However, the claims, in part, still read on any unspecified biological activity. Applicant's arguments filed 31 October 2005 have been fully considered but they are not persuasive.

For example, claim 1 reads on an epidermal growth factor polypeptide having at least 90% amino acid identity to SEQ ID NO: 1 and having epidermal growth factor biological activity in cell proliferation or receptor binding that is greater than the biological activity of the polypeptide of SEQ ID NO: 1. "The biological activity" of SEQ ID NO: 1 is still undefined and indefinite. The language of the claim that remains a concern has been emphasized. Claims 4-7 contain similar language.
Similarly, claim 3 reads on the epidermal growth factor of claim 1, wherein said polypeptide has a biological activity that is at least two times greater than the biological activity in cell proliferation or receptor binding of the polypeptide of SEQ ID NO: 1. The language of the claim that remains a concern has been emphasized. The phrase "a biological activity" is indefinite and reads on any biological activity and not merely the two biological activities delineated in claim 1. Claim 2 is rejected as depending from a rejected claim.

Claim Rejections - 35 USC § 102

9. The rejection of claims 1-7 under 35 U.S.C. 102(a) as anticipated by Coco *et al.*, (Nat Biotechnology 2002, 20(12):1246-50, previously cited in the Office Action of 5 August 2005), is maintained for the reasons of record in the Office Action of 5 August 2005 and as stated herein.

A Declaration by co-inventor Pienkos has been submitted under 37 CFR 1.132, but has not been entered. The Declaration filed under 37 CFR 1.132 on 31 October 2005, has been fully considered, but is not persuasive to overcome the rejection of claims 1-7 based upon anticipation by Coco *et al.*, because the Declaration is merely a sworn statement of derivation of work and lacks any statement to disavow the

work of others (*i.e.* the co-authors who are not inventors) identified as co-authors in the paper by Coco *et al.*

Where the applicant is one of the co-authors of a publication cited against his or her application, he or she may overcome the rejection by filing an affidavit or declaration under 37 CFR 1.131. Alternatively, the applicant may overcome the rejection by filing a specific affidavit or declaration under 37 CFR 1.132 establishing that the article is describing applicant's own work. An affidavit or declaration by applicant alone indicating that applicant is the sole inventor and that the others were merely working under his or her direction is sufficient to remove the publication as a reference under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). See MPEP 715.01(c).

Additionally, Applicants argue that the publication by Coco *et al.* did not describe the sequence of the polypeptide EGF0021, but instead mentioned only its name. Applicants argue that such a description does not satisfy the requirement that a reference must be enabling. Applicants' arguments have been fully considered but they are not persuasive.

As stated in the Office Action of 5 August 2005, while the reference does not explicitly teach the amino acid sequence of SEQ ID NO: 2, it is well established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. No evidence has been submitted showing that the protein EGF0021 taught by the Coco *et al.*, publication is not the same as the EGF21 (SEQ ID NO: 2) of the instant application. Therefore, absent evidence to the contrary, the prior art discloses exactly what is claimed in the instant application.

Moreover, although the 37 CFR 1.132 Declaration of co-inventor Pienkos was found to be unpersuasive to overcome the prior art rejection, for the reasons stated *supra*, the Declaration contains the sworn statement by a co-inventor that "the relevant disclosure in the publication was obtained from our invention." Thus, the argument of Applicants' representative that the description of the polypeptide EGF0021 in the Coco *et al.*, publication is not enabling, inferring that it is not the same polypeptide as instant SEQ ID NO: 2, is contradictory to the sworn statement of a co-inventor.

The rejection of claims 1-7 under 35 U.S.C. 102(a) as anticipated by Coco *et al.*, (Nat Biotechnology 2002, 20(12):1246-50), is maintained for the reasons of record in the Office Action of 5 August 2005 and as stated herein.

NO CLAIM IS ALLOWED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW

Brenda Brumback
BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600